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Perspective

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LifeTime aims to track, understand and target human cells during the onset and progression of complex diseases and their response to therapy at single-cell resolution. This mission will be implemented through the development and integration of single-cell multi-omics and imaging, artificial intelligence and patient-derived experimental disease models during progression from health to disease. Analysis of such large molecular and clinical datasets will discover molecular mechanisms, create predictive computational models of disease progression, and reveal new drug targets and therapies. Timely detection and interception of disease embedded in an ethical and patient-centered vision will be achieved through interactions across academia, hospitals, patient-associations, health data management systems and industry. Applying this strategy to key medical challenges in cancer, neurological, infectious, chronic inflammatory and cardiovascular diseases at the single-cell level will usher in cell-based interceptive medicine in Europe over the next decade.

While advances in medicine have led to spectacular progress in certain disease areas, most chronic disorders still partially or totally escape cure. This is mainly because most diseases are only detected late once gross physiological symptoms manifest themselves, when tissues and organs have often undergone extensive or irreversible changes. At this stage, the choice of interventions is typically quite limited. It is difficult to predict if a patient will respond to a particular treatment, which often involve invasive or aggressive therapies that can be of modest benefit, or if therapy resistance emerges leading to relapse. The reason for this is that despite technology-driven revolutions that enable a patient's physiology to be investigated at the level of molecules[1,2] and placed in the context of tissues[3,4] in most cases our detection and predictive power is limited by our incomplete mechanistic understanding of disease at the cellular level.

Cells develop and differentiate along specific lineage trajectories forming functionally distinct cell types and states[5], which together with their neighbouring cells underlie and control normal physiology (Fig 1). However, we have not been able to systematically detect and understand the molecular changes that propel an individual cell along these trajectories during normal development or ageing nor the molecular causes that trigger deviations from healthy trajectories and drive cells and tissues towards disease (Fig 1). Timely detection and successful treatment of disease will depend crucially on our ability to understand and identify when, why, and how cells deviate from their normal trajectory. More accurate cellular and molecular diagnostics will enable us to intercept disease sufficiently early to prevent irreparable damage. To achieve this interceptive medicine (Fig 1), we need to invest in approaches that provide a detailed molecular understanding of the basis of disease heterogeneity in tissues, with sufficient molecular, cellular and temporal resolution.

Several challenges need to be overcome to reveal the complex disease landscapes comprised of vast numbers of potential cellular states (Fig 1). Firstly, we need to resolve normal cellular heterogeneity across space and time to begin to determine the cell types, states and cell-cell interactions in the body. This is a main goal of the Human Cell Atlas consortium[6]. However, to discover the cellular basis of diseases requires that we track cellular heterogeneity and molecular composition of cell trajectories in health and during disease progression *longitudinally* - throughout a patient's lifetime ("LifeTime"). Secondly, we need to understand the molecular mechanisms and complex networks that define a

Affiliations appear at the end of the paper.

cell's state, and control its function, fate and trajectory over time to be able to reconstruct a cell's history and predict its future. This is essential for selecting the optimal intervention for an individual patient. Thus systematic and longitudinal profiling of samples from many patients is required. Third, computational frameworks for integrating temporal data as well as patient profiles with large cohorts to identify regulatory changes and to dissect the causes and manifestations of disease remain elusive. Current attempts to model human disease have not succeeded in integrating the thousands of molecular phenotypes that are acquired from patients. Finally, we are limited by our lack of knowledge of the underlying causes of disease. Any given patient's response to a specific therapy may require testing or modifying cells from the patient in an experimental system, a challenge yet to be routinely implemented.

To address these challenges experts from different disciplines came together in 2018 to form the LifeTime Initiative (https://www.lifetime-initiative.eu). It has since grown to be a pan-European community consisting of over 90 research institutions with the support from 80 companies, several funding agencies and national science academies. In 2019 the initiative was awarded a Coordination and Support Action by the European Commission to develop a Strategic Research Agenda (SRA)[7] for a large-scale long-term initiative with a roadmap for implementing cell-based and interceptive medicine in Europe in the next decade. The ambitious goal is the early detection and interception of complex diseases as well as being able to select the most effective therapeutic strategy for a patient. Between March 2019 to June 2020 the initiative established several multi-disciplinary working groups (listed in supplementary information), organised numerous workshops, meetings and surveys (and thus engaged the wider community) and commissioned stakeholder interviews and an impact study. The European Commission will use LifeTime's SRA during the planning of the next research and innovation framework programme - Horizon Europe. Here, we outline LifeTime's vision and key aspects of the SRA towards establishing cell-based interceptive medicine.

Central to LifeTime's vision and approach is the development and integration of novel technologies, such as single-cell multi-omics and high-content imaging, artificial intelligence (AI) and patient-derived experimental disease models. Applying these integrated approaches to address medical challenges and incorporating them in both experimental and clinical workflows is expected to directly benefit patients. For example, appropriate single-cell based biomarkers will precociously alert physicians that a cell or tissue is entering a disease trajectory. Understanding disease heterogeneity at the cellular level and knowing the molecular aetiology of a disease will allow the systematic identification of drug targets, resistance mechanisms or define therapeutic approaches, based on a given disease's molecular or cellular vulnerability. This strategy differs significantly from the classical approaches in drug discovery[8]. The stratification of patients based on underlying disease mechanisms, assessed *in situ* within single cells, will help physicians select the most appropriate treatment(s) or employ combination therapies that are tailored to the individual. These will be used first to identify cells that are deviating from the healthy trajectory, to steer them away from disease, and later to reduce the threat of relapse (Fig 1). This transformative single-cell data-driven approach has the potential to increase the success rates of clinical trials as well as the efficiency of novel therapeutic interventions in clinics over the next decade. Overall, the LifeTime strategy is likely to impact both diagnosis and treatment, improve health and quality of life dramatically and alleviate the societal burden of human diseases such as cancer, neurological disorders, infectious diseases, chronic inflammatory and cardiovascular diseases.

Below, we outline the technology development and implementation at the heart of LifeTime's approach, describe LifeTime's mechanism to identify medical priorities, discuss required infrastructures in Europe, interactions with industry and innovation, ethical and legal issues, LifeTime's education and training vision, and estimate the expected impact of the LifeTime approach on medicine and healthcare. LifeTime builds on and will collaborate with related international initiatives that are paving the way by producing reference maps of healthy tissues in the body, such as the Human Cell Atlas (HCA)[6] and the NIH Human Biomolecular Atlas Program (HuBMAP)[9].

Technology development and integration

Single-cell technologies, particularly transcriptomics, are generating the first reference cell atlases of healthy tissues and organs, revealing a previously hidden diversity of cell subtypes and functionally distinct cell states[6]. Single-cell analyses of patient samples are beginning to provide snap-shots of the changes in cell composition and pathways associated with diseases including cancer[10–15], chronic inflammatory diseases[16,17], Alzheimer's disease[18–20] heart failure[21], and sepsis[22]. Since pathophysiological processes within individual cells involve different molecular levels, understanding the underlying mechanisms requires the integration of current single-cell approaches. LifeTime proposes the integration of several approaches[7]. This includes combining transcriptomics (Fig. 2) with methodologies that provide additional information on chromatin accessibility, DNA methylation, histone modifications, 3D genome organisation, and genomic mutations[23–25]. Future developments will enable the incorporation of single-cell proteomes, lipidomes, and metabolomes, adding crucial insight into different cellular states and their roles in health and disease. In addition to specific cell subtypes and the role of cellular heterogeneity, investigating the surrounding tissue context and organ environment is crucial. New spatial -omic approaches, particularly spatial transcriptomics, include information on the location of diseased cells, their molecular makeup and aberrant cell-cell communication within the tissue[26–32]. Novel advanced imaging approaches also now enable systematic spatial mapping of molecular components, *in situ*, within cells and cells within tissues[28,33–37]. The cellular context with respect to different immune and stromal cell types, extracellular components and signaling molecules that contribute to disease progression will help identify the roles of specific cell types and interactions in diseases[32,38–40]. The implementation of cell lineage tracing approaches[41], which link cellular genealogies with phenotypic information of the same cells, may help us understand how populations of cells develop dynamically to form the specific architecture of a healthy or a diseased tissue.

LifeTime proposes to develop necessary single-cell methodologies and end-to-end pipelines (Fig 2) that will be integrated into robust, standardised multi-omics and imaging approaches, and scaled to profile hundreds of thousands of patients' cells[7]. This will require an in-depth analysis of longitudinal human samples obtained from patients and cohorts, including European and national clinical trial groups as well as initiatives collecting longitudinal biological material connected to well-annotated clinical information (Fig 3). Linking these data to clinical outcomes will identify the cellular parameters that are permissive to a therapeutic response, for example during checkpoint blockade immunotherapy[12,42,43] or treatment of multiple myeloma[11]. By detecting rare drug resistant cells that are present prior to[11,44] or that emerge during treatment[45], therapeutic regimens and combinatorial treatments can be adapted to improve outcome.

Handling these large molecular datasets will require sophisticated and distributed computational and bioinformatics infrastructures, (see Implementation and Infrastructure), as well as the development of tools to integrate and ensure interoperability of different data types, including single-cell multi-omics, medical information and electronic health records. LifeTime will work with ongoing European and national efforts for integrating molecular data into electronic health records and to establish standards and interoperable formats to address specific disease challenges. This will promote the development of advanced personalised models of disease. To be able to implement routine longitudinal sampling of patients approaches need to be developed for sampling small biopsies, including liquid biopsies, that will detect

individual cells or cell-free DNA released from pathological cells before and during therapy[46]. Multi-dimensional descriptors of cell states from patients taken from different stages of disease or therapy will be used to derive new biomarker sets or enhance current panels. Collaboration with ongoing atlas projects, industrial partners and regulatory authorities, will be key for benchmarking and deriving the new standards that will enable us to deploy these new methods in the clinic. This will hopefully achieve earlier disease detection and guide the appropriate selection of drug targets and therapies (Fig 3).

Unlocking the potential of unprecedented amounts of integrated digital information (including molecular data describing how individual cells make decisions) requires AI, in particular machine learning approaches that can identify meaningful molecular patterns and dependencies in the datasets[47,48]. Although such approaches have proven very useful when applied to medical imaging data and have enabled the identification of subtle disease-associated changes[49], medical imaging cannot capture the full complexity of human physiology nor the status of the disease at the single-cell level. High-content imaging, together with gene expression profiling, chromatin states, protein and metabolic parameters will contribute to the stratification of disease phenotypes. Machine learning and advanced modelling approaches will be used to integrate and analyse the different layers of cellular activity, and can generate multi-scale and potentially even causal models that will allow us to infer regulatory networks and predict present and future disease phenotypes at the cellular level[47,50–52] (Fig 2).

The deep integration of machine learning technologies with spatial multi-omics and imaging technologies and data has the potential to usher in a new age of digital pathology to aid the decision-making process of physicians (Fig 3). By considering not only anatomical, physiological and morphological aspects, but also multidimensional molecular and cellular data, it will be possible to provide a more granular representation of a patient's disease state to complement the pathologist's slides and bulk measurements in tissues (e.g. mRNA, metabolites). We envision as the final goal the incorporation of new AI-based decision-aiding systems that will integrate and interpret available molecular, cellular, individual disease trajectory and imaging information. Importantly, interpretable and accountable AI systems will also provide the basis for clinical recommendations. Integration of cellular information should lead to a more precise description of a patient's molecular and physiological history, and will guide early detection, allow predictive prognosis, and guide recommendations for therapeutic interventions to deliver more precise and effective treatments (Fig 3).

Understanding the cellular origin and aetiology of disease from a patient-centered perspective requires systems that faithfully recapitulate key aspects of a patient's pathophysiology, and render them experimentally tractable to test mechanistic hypotheses and predictions. Organoids are an emerging experimental system that allow modelling aspects of organ development, regeneration and pathophysiology[3,4,53] (Fig 2). Derived from adult or pluripotent human stem cells, organoids can capture individual features that are unique to each patient and can be interrogated molecularly in space and time. Importantly, by comparing organoid models from diseased and healthy individuals, unique disease features can be extracted even without knowing the specific genetic cause of the disease. Therefore, organoid models offer a unique tool for achieving some of the main goals of LifeTime, especially in cases where repeated access to patient tissues is limited or impossible, for instance for neurological disorders.

Despite their promise organoids still require significant development to harness their full potential for disease modelling (Fig. 2). LifeTime proposes to advance the models to capture the full degree of cellular heterogeneity, tissue-specific structural and metabolic conditions[54], incorporation of key physiological aspects, such as immune response, vascularisation or innervation. Because complex interactions between multiple tissues and organs are involved in many diseases, it will be necessary to develop novel tissue engineering principles that combine multiple organoids in pathophysiologically relevant crosstalk (organoid-on-a-chip). To optimise translational potential, LifeTime will engage in standardising, automating and scaling organoid approaches, allowing for systematic derivation, propagation and banking. Such industrialisation is also needed for large scale chemical or genetic perturbations (e.g. CRISPR-Cas screens), and for elucidating the genetic basis for disease variability and drug response at population-relevant scales, in both the preclinical and clinical context (Fig 3). The resulting mechanistic dissection enabled by large-scale perturbations will be used to validate corresponding AI models of disease interception and progression.

In addition to organoids, *in vivo* model systems are necessary to translate the science from bench to humans. A complex biological system is required to study the myriad of host-disease and pathogen interactions associated with complex diseases, such as infectious diseases, cancer or Alzheimer's disease. The use of animal models is important for understanding the very complex temporal relationships that occur in disease such as those involving the vasculature, immune system and pathogens as well as neuronal networks in the brain. LifeTime will therefore improve their clinical relevance and make use of models in which patient-derived tissues can be integrated into *in vivo* models[55–59] to study dynamics of cellular heterogeneity in space and time.

LifeTime, as a community, has the capacity to develop and integrate these technologies, that often require expertise and specialised instrumentation located in distinct laboratories. A coordinated effort can achieve the required benchmarking and standardisation of technologies, workflows and pipelines. This will also ensure that the data, software and models generated adhere to Findable, Accessible, Interoperable, and Reusable (FAIR) principles[60] (see infrastructure below), are available across national borders, and are in full compliance with international legislations such as the European General Data Protection Regulation (GDPR). Moreover, LifeTime will ensure that technologies, including AI and organoids, will be developed in an ethically responsible way in collaboration with patients, putting the patient at the centre. (see Ethical and Legal Issues).

LifeTime disease Launchpad to identify medical priorities

LifeTime has initiated a mechanism, called Launchpad, to systematically identify medical challenges that can be addressed through LifeTime's approach and have a direct impact on patient care. Initially, the focus has been on five disease areas that are a significant burden to society: cancer, neurological disorders, infectious diseases, chronic inflammatory diseases as well as cardiovascular diseases. Importantly, other disease areas will be continuously monitored, for example rare Mendelian diseases and metabolic diseases, and research programmes initiated as technologies and infrastructures develop. The LifeTime Launchpad has defined several criteria to identify the medical challenges. These include: societal impact (including incidence and prevalence, disease severity, economic impact and the pressing need for new and more efficient clinical treatments and early detection), evidence for cellular heterogeneity that limits current clinical avenues, availability of samples from biobanks, relevant preclinical models, existence of patient cohorts including those enabling longitudinal studies, clinical feasibility and ethical considerations, as well as alignment with national and EU funding priorities. Subsequently, multidisciplinary working groups, including clinicians, in each disease area have used these criteria to define the following disease challenges and develop ten-year roadmaps to address them in the LifeTime Strategic Research Agenda[7].

Despite cancer broadly covering hundreds of individual tumour types, there are critical knowledge gaps that are common for all cancer entities, including early dissemination and therapy resistance.

Metastatic dissemination of a subpopulation of cancer cells is a leading cause of death in almost all cancer types. Successful treatment of advanced and metastasised forms of cancer remains difficult, despite the development of targeted therapies and immunotherapies, due to the emergence of drug or therapy resistance. To address these medical priorities LifeTime recommends focusing on understanding the cell types and states - malignant cells and their microenvironment - involved in early stages of cancer dissemination and the reprogramming of cellular states during disease and their impact on therapy resistance.

For neurological disorders a major challenge is a lack of understanding of the early events in disease onset to enable the development of disease modifying therapies. The lack of access to longitudinal samples from patients requires the establishment of cohorts of patient-derived disease models to understand the cellular heterogeneity associated with disease. Discovering pathways and biomarkers for the stratification of patients based on the cellular mechanisms driving the disease will enable new design of clinical trials to reevaluate drugs previously tested without such stratification and broaden the drug target portfolio.

As seen during the COVID-19 pandemic it is important to be able to understand infection mechanisms and the host response to rapidly identify the most likely effective treatment. At the same time the continuous rise of antimicrobial resistance requires the discovery of novel therapeutic strategies. A key medical challenge for infectious diseases is to understand the cellular response to infections and develop novel precision immune-based therapeutic strategies to combat infections.

The high burden of chronic inflammatory diseases is due to long-term debilitating consequences resulting from structural destruction of affected organs or tissue. Current therapies only treat the symptoms and do not cure or fully control the chronic inflammatory pathophysiology. While many different targeted therapies exist, they are expensive and are limited by high rates of non-response to treatment. Consequently, there is an urgent need to explore and understand how cellular heterogeneity contributes to the pathology of inflammatory diseases[61,62] and how this relates to the predicted course of disease and response of a patient to one of the numerous available therapies.

Many cardiovascular and metabolic diseases lack effective therapies due to a lack of knowledge of the underlying causes and the link between abnormal cardiac cell structure/function and pathophysiology. The identified medical priority is to understand cellular and molecular mechanisms involved to enable early diagnosis and to design new mechanism-based therapies for precise clinical treatment.

The LifeTime disease roadmaps can be divided broadly into three phases[7]: firstly, immediate research into the identified medical challenges using established, scaled single-cell technologies, computational tools and disease models; secondly, the development of new technologies required to address specific medical challenges, including the development of spatial-multi-omics and imaging approaches and advanced patient-derived model systems for longitudinal analyses; finally, applying these next-generation technologies for longitudinal analyses of patient samples, or patient-derived models, combined with machine learning to generate patient trajectories and predictive models of disease. Resulting predictions and biomarkers would be validated in prospectively collected patient cohorts within clinical trials also including longitudinal liquid biopsies. The routine clinical use of predictors and biomarkers for risk stratification of patients and resulting interventions - where feasible - is the pre-final step. The final step is the extension of predictors and biomarkers to the analysis of large longitudinal patient cohorts such as national cohorts for developing secondary and tertiary prevention approaches based on the new biomarkers.

During implementation of these roadmaps the initiative will establish an experimental design working group to develop systematic procedures to ensure that the research samples acquired cover diverse subjects including age, sex-and-gender-in-research dimension and ethnicity. This will require the development of strict criteria for the inclusion of samples and ensure appropriate coverage of critical metadata. They will also define standardised procedures for acquiring and processing of samples from different pathology sites (depending on the disease area). It is envisaged that during disease challenge pilot projects an experimental design oversight body will determine, based on early data, the number of diseases that should be studied as the initiative develops with recommendations on appropriate sample sizes required to obtain sufficient statistical power.

Implementation and Infrastructure

The scale of the data that will be generated and analysed, the cross-disciplinary and international structure combined with the ambition of LifeTime to pioneer novel analytics using AI, places LifeTime in an excellent position to shape the next generation of European medical and biological data computational infrastructure. This will require close interaction with and evolution of the established European infrastructure (Fig 4), such as the European Open Science Cloud (EOSC) and high-performance computing infrastructures through EuroHPC. LifeTime will also interact with related European Life Sciences Research Infrastructures[63] to create added value and to avoid duplication of efforts in strategies and tools for sharing and accessing data, development and application of standards. As medicine is inherently decentralised, LifeTime will also contribute to connecting EU medical systems and large centralised European data infrastructures.

Fragmentation of research across borders, disciplines and timeframes needs to be overcome. LifeTime data generation and technology development will be harmonised across expert groups and centres, allowing results to be quickly applied in clinics. Thus, a coordinated approach is required that integrates the multidisciplinary expertise of single-cell technologies, data science, and organoids/*in-vivo* models across Europe. It must also engage clinicians and patients to achieve medical impact. To address these challenges, LifeTime proposes a multidisciplinary network of LifeTime Centres (Fig 4) with different complementary thematic clusters across Europe, each working in close association with hospitals. These connected, flexible innovation nodes will share resources, gather the necessary critical mass for global competitiveness, and be open for collaboration with the entire scientific community. Importantly, LifeTime Centres should deliver a number of key functions:

- Serve as platforms for the development and advancement of breakthrough technologies for single-cell research in omics and imaging, AI/machine learning and experimental/computational disease models.
- Closely and actively collaborate with patients, clinicians, hospitals and healthcare systems, in some cases with a specific disease focus.
- Set standards in data generation, standardisation and management implementing FAIR principles.
- Set standards in ELSI programmes (ethical, legal and societal issues) by working together in multidisciplinary teams aimed at responsible research and innovation.
- Offer opportunities to collaborate, test and benchmark new methodologies and analysis methods e.g. in adaptive experimental design.
- Offer unique opportunities to industry to translate recent knowledge and novel technologies from the laboratory to the market.
- Provide an early access programme to new technologies developed by companies.
- Function as open, interconnected education hubs, delivering training in the new technologies to researchers, scientific personnel and clinicians, as well as provide engagement activities for patients and citizens.

LifeTime aims to analyse data which is inherently distributed across different clinical centres in different countries, which is a significant challenge. These data are usually not accessible outside a national, regional clinical care system or specified data 'safe havens', when they

are accessible accredited systems are often required for storing the data and information governance may be at the hospital, federal or international level. This means that a federated approach is the only way to access and integrate information from various European healthcare systems. Thus, the LifeTime data and computational network building on cloud technologies will provide the necessary capacities to enable federated analytics across the LifeTime centres and will provide a technical and legal framework for integrating core information structures, multi-omics assays, imaging, AI/machine learning technologies and health records (Fig 4). A joint Data Coordination Centre following a multi-level approach will ensure transparent data access control, compatibility and standardisation. Within this framework LifeTime will also coordinate and pioneer open data sharing and reuse and collaboration, including access models prior to publication of data.

To start this cooperative LifeTime Centre network, the initiative can build on first initiatives by LifeTime members in a number of European countries, examples are the VIB Single-cell Accelerator Programme in Belgium, the Berlin Cell Hospital/Clinical Single-cell focus in Germany, the UK's Sanger/EBI/Babraham Single Cell Genomics Centre, or the LifeTime Single-Cell Centre in Poland, to name a few. To avoid duplication and lack of standardisation, the LifeTime Cell Centre network should be coordinated through an entity or framework that optimises coordination and support to achieve the LifeTime vision. Funding for specific research projects that involve one or more LifeTime Centres could come from a portfolio of private and public funding opportunities, both on the national and pan-European level. The network will closely interact with key European efforts and will contribute to EU strategies and programmes.

Interaction with industry/innovation framework

Collaborations with the private sector will be key for rapid translation and delivery of technologies, instrumentation, diagnostics and therapies (Fig 4). Currently over 80 companies support LifeTime's vision. These span multiple sectors as well as industrial associations and networks such as the European Federation of Pharmaceutical Industries (EFPIA), and the Euro-BioImaging Industry Board (EBIB).

Transforming breakthrough discoveries into solutions to improve the health of European citizens involve several crucial steps. These include creating a unifying framework that fosters and streamlines pre-competitive interactions between academia and industry at the interface of computer science, single-cell biology, -omics, imaging, patient-derived disease modelling and precision medicine. A large-scale collaboration platform across Europe should be developed that provides umbrella agreements, regular physical meetings, dual training of early-career scientists in academia and industry, as well as exchange programmes. This will enable joint projects between public and private sectors spanning the entire biomedical innovation cycle from discovery research, technology development and implementation in hospitals and the healthcare industry.

Cross-sectoral collaborations between small, medium-size and large companies with different development timelines and distinct business models is crucial to stimulate innovation. To expedite the identification of, and investment in the emerging technologies developed in academic and industry laboratories, successful local initiatives such as tech watch and accelerator programmes (e.g. the VIB Single-cell Accelerator) should be scaled and coordinated at the EU level. LifeTime aims to create a networking/match-making platform for individuals, academic and industry organisations that share the goal of developing and integrating breakthrough technologies and applying them in the clinic to benefit patients. Further measures could foster innovation and entrepreneurship. For example, a pre-seed, pre-incubator funding scheme based on competitive calls to support start-up or tech transfer ideas.

Creating a dedicated European ecosystem is also essential. Achieving this requires additional key measures such as the development of enabling digital environments, promotion of early disease interception with all necessary stakeholders (patients, regulators, payers, etc.) as described in the LifeTime call for action launched in December 2019 (https://lifetime-initiative.eu/make-eu-health-research-count/).

Ethical and Legal Issues

The implementation of LifeTime's vision triggers relevant ethical questions from all societal groups directly impacted by the project (patients, clinicians and scientists), and society in general. LifeTime aims to pioneer a real-time or parallel ELSI (ethical, legal and societal issues) programme that will predict, identify, monitor and manage the ethical impact of the biomedical innovations that arise from research and technology development, ensuring that implementation follows ethical guidelines. LifeTime's ELSI programme can be used as a testing ground for other international interdisciplinary initiatives (Fig 4). Ethical issues will be identified and managed as early as possible and ensure that ethical and research integrity guidance is implemented throughout the entire research process to stimulate positive effects and mitigate negative ones[64].

Specialists in bioethics, public engagement, ethics of technology and lawyers have identified LifeTime's ethical and societal priority areas. These include questions related to the derivation, storage and use of organoids, the use of AI, data ownership and management, anonymisation of data, equity of access to such revolutionary medical care, the definition of health and illness, and transparent science communication to society[65]. Initiating a relationship of trust with citizens will include diverse modes of communication and engagement, for example through art, citizen science and public dialogue, contributing to scientific literacy, and promoting individual critical thinking and public participation in decision-making processes.

Education and Training

Introducing interceptive medicine into clinical practice in parallel with a multidisciplinary research programme will require capacity building in health and research systems, and significant technology deployment in the clinics. This will lead to a collaborative, fast-developing and interdisciplinary environment in research and in the clinics, requiring new training inputs. To respond to these needs, LifeTime will create an Education and Training Programme, ensuring the sustainable application of new technologies and implementation of new medical and scientific approaches (Fig 4). Importantly, this will be done in an integrative scheme, intersecting the multiple LifeTime disciplines and areas of actions: disruptive technologies applied to medical challenges, technology transfer and innovation, research integrity, data management and stewardship, ethical and societal issues, communication and emotional skills, or management of medico-scientific and collaborative projects.

Each LifeTime training activity will be based on multi-lateral education: basic researchers will teach other researchers and clinicians about the potential of the technological solutions, while clinicians will teach researchers about clinical needs and biological challenges of the diseases in focus. This will strictly follow the idea of bench to bedside and back. The programme will have an inclusive philosophy to ensure that it can provide training to the wide community, including researchers, clinicians, technical operators, managers and staff of technology platforms, as well as administrators, patients and the lay public.

LifeTime envisions the organization of cycles of colloquia and outreach activities to inform the public, the formulation of short-term courses compatible with a culture of lifelong learning and adaptability, as well as interdisciplinary Masters and PhD programmes. Through education and training, LifeTime will engage and inform society, will develop new professional curricula and will train a new generation of highly skilled medical scientists and support staff, in order to foster scientific and medical excellence in an ethical, responsible and inclusive framework.

Impact on Medicine and Healthcare

Medicine and healthcare are rapidly expanding pillars of our economy. EU countries collectively spend more than €1,400 billion per year on healthcare for their 500 million citizens. Given the dimensions and spiraling healthcare costs associated with an ageing population, these numbers will continue to increase unless we can mitigate the damaging effects of ageing. We expect that coupling the current health monitoring with early detection and disease interception, will have a major economic impact. In Europe, 20% of the population will soon be over 65, with an age distribution that will continue to change until 12% are over 80 in 2080[66]. Given the prevalence and cost of caring for people with degenerative conditions and the increase in chronic lifestyle-induced diseases, the knowledge and technologies developed by LifeTime will allow us to detect them earlier, and avoid their worst manifestations. LifeTime would also have an impact in the era of unexpected pandemics such as COVID-19 by rapidly determining the cellular and molecular basis of the disease. This would identify potential therapeutic strategies for patient subgroups as well as starting point for the development of new efficient therapies.

One of healthcare's largest outstanding issues is that many patients do not respond to commonly prescribed treatments. Whereas well-controlled randomised clinical trials provide evidence for statistical utility of a given therapy, in actual practice often many patients must be treated before a single patient will show a measurable benefit. Other patients may not benefit at all or even be harmed[67] leading to an economic loss that is estimated to be in the hundreds of billions €/year. The variable therapeutic responses originating from the cellular and genetic heterogeneity that exists in cancer and other complex diseases, contributes not only to the failure of treatments, but also to the rising cost of drug development, which is currently estimated at ~€1-2 billion per drug. *In silico* models for disease trajectories generated by LifeTime will enable the integration of personal genetic and lifestyle information into predictive models of disease course. This will allow physicians to determine and implement optimal therapeutic strategies tailored to the individual (precision medicine) with sophisticated timing of disease interception. The knowledge gained will also contribute to a more appropriate selection of patients for clinical trials.

Outlook Summary

Recent advances in key single-cell technologies, AI and patient-based experimental systems, such as iPS and organoids, have set the stage for their integration and deployment to improve mechanistic molecular understanding, prediction, and treatment of disease onset and progression. Patients will benefit from cell-based medicine though the earlier detection of diseases at a stage where they can be effectively intercepted. The novel, integrated technologies will enable the selection, monitoring and, if necessary, modification of therapeutic strategies for an individual to improve clinical outcomes based on high-resolution cellular information. Within the next decade, the obtained molecular mechanistic information has the potential to revolutionise drug discovery processes, clinical trial design, and eventually be incorporated into clinicians' daily decision-making processes. As the LifeTime community continues to grow, new individuals, institutions and companies are encouraged to join and contribute to establishing a European platform to implement single-cell and data-driven medicine to address the growing burden of complex and chronic diseases.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2715-9.

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Competing interests C.B. is an inventor on several patent applications in genome technology and cofounder of Aelian Biotechnology, a single-cell CRISPR screening company. H.C. is a non-executive board member of Roche Holding, Basel. A.P. holds European and US patents on "Genome Architecture Mapping" (EP 3230465 B1, US 10526639 B2). W.R. is a consultant and shareholder of Cambridge Epigenetix. T.V. is co-inventor on licensed patents WO/2011/157846 (Methods for haplotyping single cells), WO/2014/053664 (High-throughput genotyping by sequencing low amounts of genetic material), WO/2015/028576 (Haplotyping and copy number typing using polymorphic variant allelic frequencies). All other authors declare no competing interests.

Additional information

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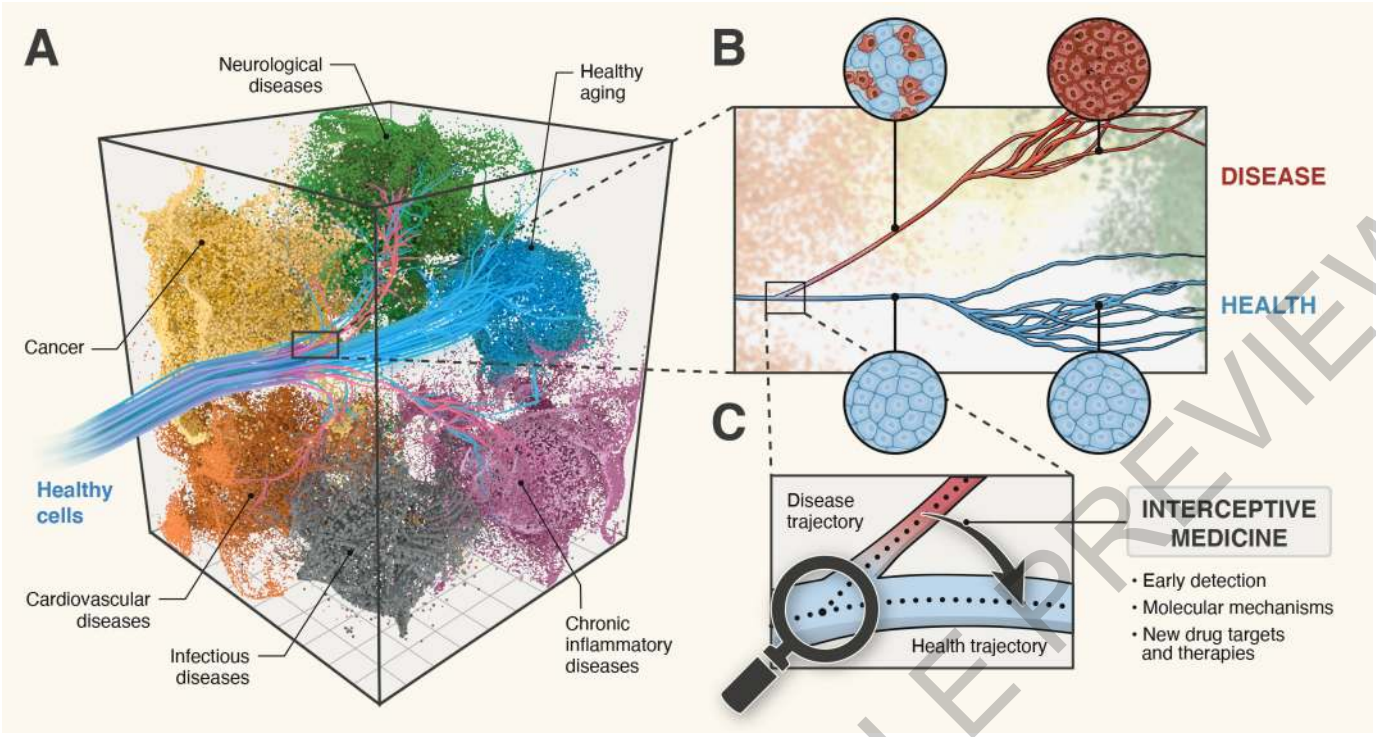

Fig. 1 | Early disease detection and interception by understanding and targeting cellular trajectories through time. (A) Cells are programmed to develop and differentiate along many different specific lineage trajectories (blue trajectories) to finally reach their functional state. When these normal lineage processes go awry, it can cause a cell to deviate from a healthy state and move towards a complex disease space (coloured manifolds defined by multi-dimensional molecular space – including gene expression, protein modifications, metabolism), as shown by red trajectories. (B) Many diseases are only detected at a relatively late state with the onset of symptoms (red trajectory) and when pathophysiological changes can be at an advanced stage (red cells). At this point, cells, tissues and organs have undergone extensive and often irreversible molecular and physiological changes since the initial events that caused them to deviate from a healthy state. Hence, the choice of interventions may be limited and often require harsh or invasive procedures. (C) Understanding the early molecular mechanisms that cause cells to deviate from a healthy to a disease trajectory will provide biomarkers for early detection of disease and new drug targets and innovative therapies to intercept diseases before onset of pathophysiology and manifestation of symptoms.

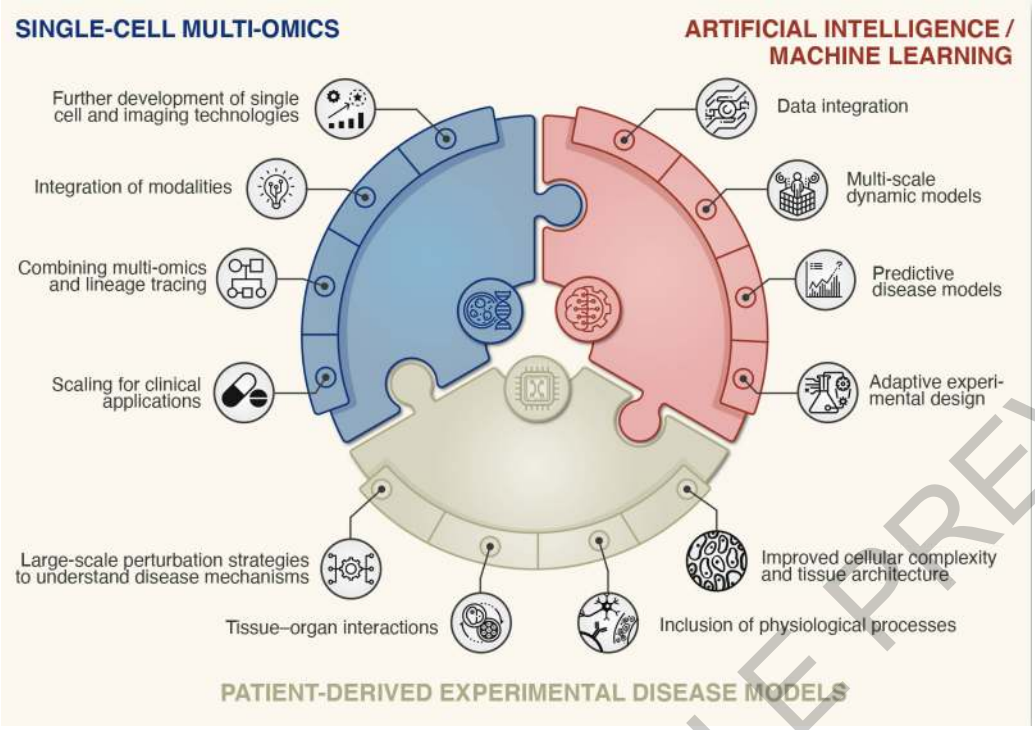

Fig. 2 | Hallmarks of the LifeTime approach to disease interception and treatment. The scheme represents the development and integration of key technologies for investigating human diseases as envisioned by the LifeTime initiative. Single-cell multi-omics and imaging technologies will be developed for high throughput applications. Different modalities are combined to provide insight into underlying mechanisms based on coordinated changes between different regulatory molecular layers. To obtain insight into cellular genealogies and cellular dynamics requires the integration of lineage tracing tools. Technologies will also need to be scaled for deployment in the clinics. Integration and analysis of large, longitudinal multi-omics and imaging datasets will require the development of new pipelines and machine learning tools. These include development of causal inference and interpretative machine learning approaches to create molecular networks for predictive and multiscale disease models. Patient-derived disease models such as organoids will be further developed to improve tissue architecture, incorporation of physiological processes, such as vasculature, nerve innervation and immune system to provide models that more faithfully recapitulate disease processes. Improved knowledge of disease mechanisms requires application of large-scale perturbation tools to organoids. Tissue-tissue and organ-organ interactions will be recreated using microfluidics and organ-on-a-chip technologies to study key systemic interactions in diseases.

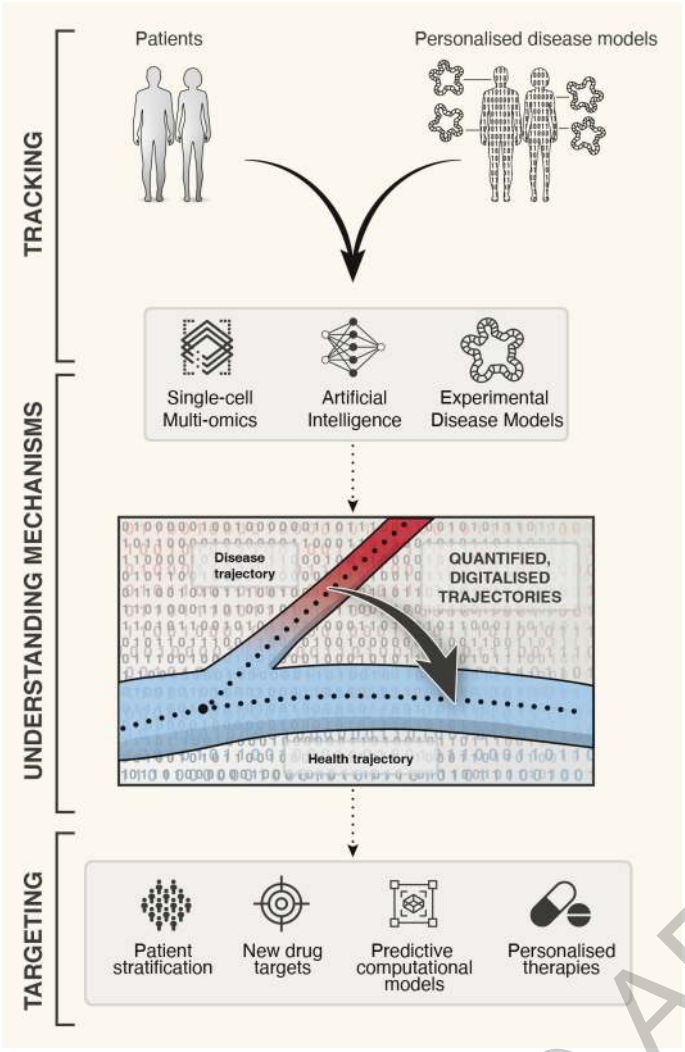

Fig. 3 | Exploiting the LifeTime dimension to empower disease targeting. Single-cell multi-omics analysis of patient derived samples (blood or tissue) or personalised disease models (e.g. organoids, experimental disease models) will be profiled longitudinally to cover the different disease stages. Large-scale multidimensional datasets will provide quantitative, digitalized information that will inform on the decision-making processes of cells. This will be analysed using AI/machine learning to arrive at predictive models for disease trajectories providing single cell resolution and molecular mechanisms of disease onset and progression. Models will be validated using large-scale perturbation analysis and targeted functional studies in disease models, which will be used in an iterative process to improve both computational and disease models.

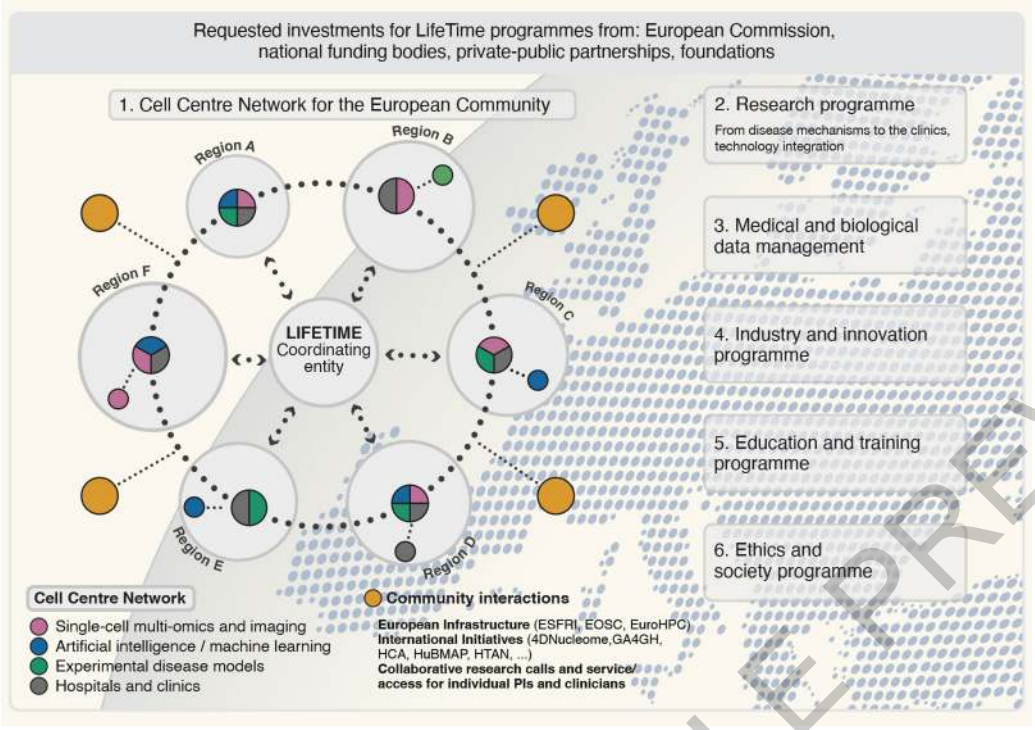

Fig. 4 | Blueprint of the LifeTime Initiative. LifeTime proposes a large-scale research initiative to coordinate national efforts, as well as foster collaboration and knowledge exchange between the public and private sector. LifeTime recommends the implementation of several programmes. (1) Network of Cell Centres to support the European Community. A network of interdisciplinary centres would complement each other's strengths and expertise in the three LifeTime technology areas and operate in tight association with hospitals, and integrate technology development with clinical practice. The connected but geographically distributed nodes would serve both as innovation hubs with strong links to industry as well as open education and training centres. Community coordination would avoid duplication of efforts and increase effectiveness requires funding instruments for a central coordination body (2) LifeTime research and technology integration programme, including both technology development and integration as well as discovering disease mechanisms and clinical applications. (3) Medical and biological data management platform. (4) Programmes fostering industry and innovation. (5) Education and training. (6) Ethics and societal engagement.